UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,520	03/08/2001	Hideo Iba	423-59	5027

7590 08/23/2002

Nixon & Vanderhye P.C.
1100 N. Glebe Road, 8th Floor
Arlington, VA 22201-4714

EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 08/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/800,520	Applicant(s) IBA ET AL.	
	Examiner Gerry Leffers	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Receipt is acknowledged of a preliminary amendment, filed 3/8/01 as Paper No. 4, in which claims 1-7 and 10-33 were cancelled. Claims 8-9 are pending in this application.

Sequence Compliance

Receipt is also acknowledged of an amendment filed 8/6/01 as Paper No. 7 in which sequence identifiers were added to sequences in the specification. The request to use the CRF from the parent application and new paper copy of the sequence listing with accompanying statement were also received (Paper No. 8). The paper copy of the sequence listing and CRF have been entered and the application is now in sequence compliance.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor.

Specification

The abstract of the disclosure is objected to because it does not address the claimed invention. Correction is required. See MPEP § 608.01(b).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of DePonti-Zilli et al (PNAS USA 1988, Vol. 85, pages 1389-1393; see the entire reference).

The Pavlakis patent (the '596 patent) teaches methods for identifying and correcting inhibitory/instability sequences (INS) within the coding region of an mRNA of a desired protein such that the level of production of the desired protein can be increased (e.g. Abstract; columns 5-6, bridging paragraph). Pavlakis et al teach that in order to evaluate whether putative regulatory sequences are sufficient to confer mRNA stability control (e.g. destabilization) on an mRNA transcript, DNA sequences coding for the suspected INS region are fused to an indicator

(or reporter) gene to create a gene coding for a hybrid mRNA. The DNA sequence fused to the indicator gene can be cDNA, genomic DNA or synthesized DNA. Examples of acceptable reporter genes known in the art are genes encoding neomycin resistance protein (note: neomycin itself is not a protein), B-galactosidase, chloramphenicol resistance, luciferase, B-globin, PGK1 and ACT1.

The '596 patent teaches that the stability and/or utilization of the mRNAs generated by fusion of the indicator genes and sequences suspected of encoding an INS region is tested by transfecting the hybrid genes into host cells which are appropriate for the expression vector used to clone and express the mRNAs. The resulting levels of mRNA are determined by standard methods of determining mRNA stability (e.g. Northern blots, S1 nuclease mapping or PCR methods), and the resulting levels of protein produced are quantitated by protein measuring assays (e.g. ELISA, western blot, etc.). The INS regions are identified by a decrease in the protein expression and/or stability of the hybrid mRNA as compared to the control indicator RNA (e.g. column 13, lines 44-62). Once INS regions of a particular target gene are identified, the coding sequence can be altered such that the expressed polypeptide is the same one encoded by the original coding sequence, or a conservative variant of the original polypeptide (e.g. column 16, section 3). Mutated or altered coding sequences designed to remove INS sequences are then tested in the same manner as was used to identify the INS sequence (e.g. column 16, lines 45-56).

The Pavlakis et al patent teaches that genes encoding or suspected of encoding mRNAs containing inhibitory/instability regions within the coding region are particularly relevant to the invention (column 12, lines 34-36). In particular, c-fos is identified as a protein whose coding

sequence is known in the art to comprise INS sequences that result in the c-fos transcript being unstable such that it is rapidly degraded (e.g. column 2, lines 8-13; column 12, lines 15-35). Example 3 is directed towards an embodiment wherein fragments encoding c-fos are operatively linked to a sequence encoding a reporter protein (i.e. RSV gag).

The Pavlakis et al patent does not explicitly teach an embodiment where the neomycin resistance gene is operatively linked to a coding sequence comprising an INS, although it does suggest that the neomycin resistance gene would be an effective reporter in their system. The '596 patent doesn't explicitly teach the fusion of a coding sequence for neomycin resistance to any part of the c-fos gene.

The DePonti-Zilli et al reference teaches the characterization of a 40 base-pair sequence in the 3' end of the B-actin gene with regard to regulating B-actin mRNA transcription during myogenesis (e.g. Abstract). DePonti-Zilli et al teach that fusion of the 40 base-pair sequence 3' to the genes for a-cardiac-actin and neomycin-resistance protein confers the B-actin mRNA regulatory pattern on the hybrid constructs when introduced into C2C12 cells (e.g. Abstract; Figure 3). Hybrid transcript levels were detected by S1 nuclease protection assays using end-labeled neomycin resistance gene probes (e.g. page 1389, column 2, "RNA Isolation and Nuclease S1 Analysis"; Figure 3). The authors conclude that although the 40 base-pair sequence from B-actin fused to the neomycin resistance coding sequence conferred B-actin transcriptional regulatory patterns on the hybrid transcript, the control was not at the level of RNA stability (e.g. pages 1392-1393, bridging paragraph). Therefore, DePonti-Zilli et al do not teach the construction and use of a short-lived transcript drug resistance gene.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the neomycin resistance gene in the methods of Pavlakis et al as an indicator to identify instability sequences (INS) of a gene encoding a transcript known or suspected to possess such INS sequences because Pavlakis et al teach it is within the skill of the art to use the gene encoding neomycin resistance as a reporter gene to identify such instability sequences and because DePonti-Zilli et al teach the use of the neomycin resistance gene to characterize a putative transcriptional regulatory sequence when the putative regulatory sequence is fused to the sequence encoding neomycin resistance. One would have been motivated to do so in order to receive the expected benefit, as suggested by Pavlakis et al and actually exemplified by DePonti-Zilli et al, of being able to characterize the ability of a putative transcriptional regulatory sequence to affect the stability/utilization of a neomycin resistance gene transcript. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the neomycin resistance gene as a marker to identify transcriptional regulatory sequences that destabilize the neomycin resistance transcript. In cases in which such a destabilizing element is identified using the neomycin resistance gene as a reporter, one would necessarily have generated a short-lived transcript drug resistance gene.

It would have been further obvious to one of ordinary skill in the art at the time of the invention to utilize the neomycin resistance gene as a reporter to identify and characterize the INS sequences within the gene encoding c-fos and to optimize c-fos expression because Pavlakis et al teach it is 1) within the skill of the art to use their methods to identify the INS sequences within a gene encoding a desired protein and to alter the INS sequences so that expression of the desired protein is increased; 2) that c-fos is a particularly relevant gene for practicing the claimed

methods; and 3) that the methods can be practiced with the neomycin gene as a reporter; and because DePonti-Zilli et al teach the use of the neomycin resistance gene to characterize a putative transcriptional regulatory sequence when the putative regulatory sequence is fused to the sequence encoding neomycin resistance. One would have been motivated to do so in order to receive the expected benefit of identifying all of the INS sequences within the c-fos transcript and optimizing expression of the c-fos protein, as taught by Pavlakis et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in using the neomycin gene as an indicator for the presence of a destabilizing INS within the c-fos transcript.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is vague and indefinite in that the metes and bounds of the phrase "...wherein the mRNA has been made short-lived by using an mRNA unstabilizing signal originating in c-fos..." are unclear. The phrase is unclear in that the words "by using an mRNA unstabilizing signal" implies a number of alternate means for utilizing such a signal to affect the stability of an mRNA. Upon reading the specification, it appears that the only way that one can "use" such a destabilizing signal to affect the stability of another RNA is by actually inserting the signal into

the target mRNA. It would be remedial to amend the claim language to clearly indicate that the unstabilizing signal obtained from c-fos has been inserted into the drug resistance gene.

Conclusion

No claims are allowed. The embodiments drawn towards the hygromycin resistance and puromycin resistance genes are not anticipated by the prior art and there is no motivation provided by the prior art to make a short-lived transcript drug resistance gene with these specific genetic markers.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
August 21, 2002